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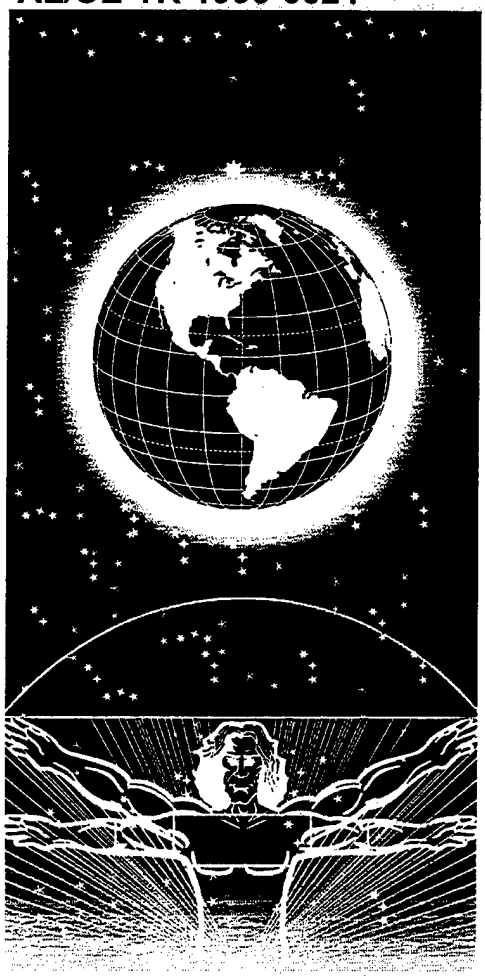

UNITED STATES AIR FORCE
ARMSTRONG LABORATORY

90-DAY NOSE-ONLY INHALATION TOXICITY STUDY OF TRIFLUOROIODOMETHANE (CF_3I) IN MALE AND FEMALE FISCHER 344 RATS

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The animal use described in this study was conducted in accordance with the principles stated in the "Guide for the Care and Use of Laboratory Animals", National Research Council, 1996, and the Animal Welfare Act of 1966, as amended.

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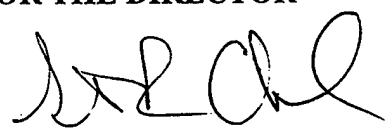

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Trifluoroiodomethane (CF3I) is being considered as a replacement for Halon fire suppressants. It's structure is similar to that of Halon 1301 (CF3Br), but it has very low ozone depletion potential. Male and female Fischer 344 rats were exposed to 0 (air only),

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SUMMARY

Trifluoroiodomethane (CF_3I) is being considered as a replacement compound for Halon fire suppressants. Its structure is similar to that of Halon 1301 (CF_3Br), but it has very low ozone depletion potential compared to CF_3Br. As part of the process to develop environmental and health effects criteria, a 90-day inhalation toxicity study was conducted. Male and female Fischer 344 rats were exposed to 0 (air only), 2, 4, or 8% CF_3I vapor, 2 h/day, 5 days/wk for 13 weeks. Exposures were conducted in nose-only chambers where animals were placed in restraining tubes during the period of CF_3I inhalation. Endpoints for toxicity assessment included clinical observations, body weights, hematology, bone marrow cell toxicity/mutagenicity (micronuclei induction), serum chemistry, organ weights, gross pathology and histopathology. Interim (30-day) and final (90-day) animal sacrifices were designed to determine and evaluate potential toxicity due to CF_3I exposure. Specific emphasis was placed on examining the thyroid, including morphometric image analysis and immunoradiometic assays for serum thyroid hormones. Male rats exposed to 8 or 4% CF_3I and female rats exposed to 8% CF_3I had lower mean body weights than the air-only control animals. Deaths observed in the 2 and 8% groups of male rats were attributed to accidents for the restraint system employed. Mild but consistent hematologic alterations in the 8% group included a reduction in red blood cell count (males only) and a reduction in total lymphocytes. Statistically significant and exposure-related increases in the frequency of micronucleated bone marrow polychromatic erythrocytes were observed in male and female rats of all three CF_3I exposure groups. The severity of the micronuclei-induction effect increased with time of exposure. Statistically significant and consistent serum chemistry alterations observed in rats of the 8% group included decreases in calcium, ALT, triglycerides (males only) and T_3; serum levels of thyroglobulin, rT_3, T_4 and TSH were increased. Similar changes in serum concentrations of thyroglobulin, T_3, rT_3, T_4 and TSH were observed also in male and female rats of the 4 and 2% CF_3I groups and occurred at both the interim (30-day) and final (90-day) animal sacrifices. At necropsy, mean organ weight values varied due to statistically significant differences in body weights between the 8% CF_3I and control groups. When expressed as a percentage of body weight, notable organ weight increases occurred in the brain, liver and thyroid; decreases were observed in the thymus and testes. A decrease in relative thymus weights and an increase in relative thyroid weights were observed also in male and female rats of the 4% group. In the 2% CF_3I group, males had a higher relative thyroid weight compared to controls, and females had a lower relative thymus weight compared to controls. Exposure-related histopathological findings of biological significance included a minimal to mild inflammation in the nasal turbinates of rats exposed to 4 or 8% CF_3I, minimal to mild atrophy of the testes and degeneration of spermatogonia in male rats exposed to 4 or 8% CF_3I, and a mild

increase in thyroid follicular colloid content in rats of all CF_3I exposure groups. The association of testicular degeneration with CF_3I exposure is equivocal due to the potential stress of the animal restraint system used throughout the study. The results from this investigation showed signs of multiple organ toxicity in rats of the 8% group. Mild to minimal toxicity extended into rats of the 4 and 2% CF_3I exposure groups. Though NOAELs were observed for select target organs (e.g., nasal turbinates, testes), NOAELs were not apparent in all target organs examined (e.g., thyroid, bone marrow).

PREFACE

This is one of a series of technical reports describing results of the experimental laboratory programs conducted at the Toxic Hazards Research Unit, ManTech Environmental Technology, Inc. This document serves as a final report on the 90-day nose-only inhalation toxicity study of trifluoroiodomethane (CF_3I). The research described in the report began in June 1994 and was completed in January 1995 under U.S. Air Force Contract No. F33615-90-C-0532 (Study No. F37). Lt Col Terry A. Childress served as Contract Technical Monitor for the U.S. Air Force, Armstrong Laboratory, Toxicology Division.

The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals*, prepared by the Committee on the Care and Uses of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council, DHHS, National Institute of Health Publication #86-23, 1985, and the Animal Welfare Act of 1966, as amended.

The authors gratefully acknowledge David L. Courson, Richard J. Godfrey, Willie J. Malcomb, and Jerry W. Nicholson for their excellent technical assistance. Also acknowledged are Latha Narayanan for the radioimmunoassays, Dr. John Grabau for the thyroid image analysis, Gerry Buttler for CF_3I analysis, Drs. S. Sharma and S. Z. Zhu for the micronuclei assay, and Dr. Darol Dodd for assistance in technical writing.

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SECTION I

INTRODUCTION

Environmental concern over the depletion of stratospheric ozone and global warming has led to an international treaty called the The Montreal Protocol (1984) which calls for the phase out of halons by the year 2000. Presently, the Air Force is using Halon 1301 (CF_3Br) as a flooding agent for extinguishing in-flight aircraft and electronic equipment fires and for fire extinguishment in confined spaces. Because it is has less ozone depleting activity and excellent fire suppression properties, trifluoroiodomethane (CF_3I) is being considered as a possible replacement for Halon 1301 in unoccupied spaces.

Little information is available in the literature concerning CF_3I toxicity. A modified acute inhalation toxicity test was performed in which rats were exposed in a nose-only chamber to 12% CF_3I for 15 min (Skaggs et al.,1993). Excess salivation was observed in the rats upon removal from the chamber; however, all rats appeared to be fully recovered by 2 h postexposure. A 15-min, nose-only inhalation study in rats determined the LC_{50} value to be 27% CF_3I (Ledbetter, 1994). No deaths occurred following an acute 4-h nose-only inhalation exposure to either 0.5 or 1.0% CF_3I (Kinkead et al., 1994). Additionally, no treatment-related signs of toxic stress were noted immediately following exposure. Histopathologic examination of select tissues from animals examined immediately following exposure, three days postexposure, or after a 14-day postexposure observation period showed no lesions of pathologic significance. No repeated exposure toxicity studies with CF_3I were found in the literature.

In other toxicity testing protocols, CF_3I was positive in the *Salmonella typhimurium* histidine reversion mutagenesis assay (Mitchell, 1995a). The L5178Y/*tk* mouse lymphoma cell mutagenesis assay showed that CF_3I did not induce gene or chromosomal mutations in mammalian cells *in vitro* (Mitchell, 1995c). However, a positive evaluation in the mouse bone marrow erythrocyte micronucleus test indicated that CF_3I was clastogenic *in vivo* (Mitchell, 1995b). Cardiac sensitization testing of CF_3I vapor using beagle dogs showed a no observable effect level at 0.2% and a lowest observable adverse effect level at 0.4% (Kenny *et al.*, 1995). This toxicity precludes the use of this compound as a flooding agent in occupied spaces, but it may still be used in unoccupied spaces (Vinegar *et al.,* 1995).

CF_3I has a high vapor pressure under ambient conditions (541 mm Hg at 25^0C), thus inhalation is a major route of exposure for persons in the workplace. The objectives of this study were to 1) obtain repeated (subchronic) inhalation exposure data in rats to assess potential target organ effects and 2) to obtain a no-observable-adverse-effect-level (NOAEL). Since CF_3I

contains an iodine atom, it is possible that CF_3I exposure might interfere with thyroid function (Capen, 1995). In this investigation, emphasis was placed on monitoring several serum thyroid hormone levels and on histopathological examination of the thyroid, including image analysis of thyroid follicular colloid

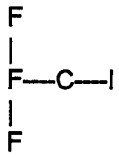
SECTION II

MATERIALS AND METHODS

Test Material

Pertinent physical and chemical properties of trifluoroiodomethane follow.

Structure



CAS No.	2314-97-8
Systematic Name	Iodotrifluoromethane
Molecular Weight	195.91
Empirical Formula	CF_3I
Physical State	Colorless gas
Specific Gravity	2.3608 g/mL (-42 °C)
Melting Point	-110 °C
Boiling Point	-22.5 °C
Flash Point	None
Flammability Limits	Nonflammable
Vapor Pressure	541 mm Hg @ 25 °C
Solubility in H_2O	0.862%

CF_3I, a liquid under pressure at room temperature, was obtained from Deepwater Iodide, Carson, CA, through Combat Systems Activity, Aberdeen Proving Ground, MD. Eleven propane tanks were received, each containing between 36 and 69 pounds of CF_3I. The purity of the CF_3I test material was determined to be 99.6+% by GCMS (Tekmar 7000 Headspace Analyzer, Forster City, CA; Hewlett-Packard 5890A GC, HP 5970B Mass Selective Detector, and HP Vectra 386/25 Data System, Palo Alto, CA). Decomposition products of CF_3I are likely to include hydrogen fluoride and hydrogen iodide. Thus, the test material was tested for the presence of fluoride ion using a Combination Fluoride Ion Electrode, Model 96-09-00, with an Orion Model 701A Digital Ionalyzer (Orion Research, Inc., Cambridge, MA). A 1-ppm (W/V) fluoride standard was used as an absorber for a 100:1 concentration of fluoride. The five cylinders used in this study contained 5 ppm or less (W/W) fluoride to CF_3I.

Exposure Chamber Design and Operation

Nose-only rather than whole-body exposures were performed, because of limited supply and high cost of the CF_3I test material. This decision reduced considerably the amount of test material required to carry out the 90-day study. The chamber selected for nose-only exposure was a stainless-steel flow past system designed by Cannon et al., 1983. Each chamber has 52 ports for exposure of animals. In this study, 30 ports were selected randomly for rat exposure. Rat restraining tubes made of Lucite® were plugged into the animal ports resulting in the outward extension of the tubes radially from the main body of the chamber.

Generation of Test Material

The CF_3I and dilution air were delivered from pressurized systems and were controlled through flow meters. Fine control of chamber concentration was made by minor adjustment of the CF_3I flow in response to chemical analysis of the chamber atmosphere. Total chamber air flow resulted in the delivery of more than 300 mL/min of mixed CF_3I/air at each animal port.

A portion of the diluent air passed through a gas washing bottle (Ace Glass, Vinland, NJ, Model 7166-26) containing water to provide adequate relative humidity to the chamber input air stream. Relative humidity and temperature of the exposure atmosphere were constantly monitored and recorded using HY-CAL dual probes (Models CT830, HY-CAL, Atlanta, GA) and a Data Acquisition system.

GC/MS analysis of mixed CF_3I/air collected from the nose-only ports did not differ from the CF_3I vapor collected from the cylinders demonstrating no breakdown products of the test material during the generation of test atmospheres.

Chamber Analysis

Continuous analysis of the chamber air for CF_3I was performed using infrared absorption spectrometers (Miran 1A, Foxboro Analytical, South Norwalk, CT). A short path (10-cm) cell in combination with a low intensity absorption band at 9.6 to 9.7 microns facilitated the analysis of the chamber CF_3I vapor concentrations involved in this study. Instrumental calibration was performed using known concentrations of freshly prepared CF_3I in air contained in tedlar sample bags (231 series, SKC, Eighty Four, PA). Calibration checks were performed at two-week intervals during the study.

Exposure Concentration Selection

In addition to the acute inhalation toxicity studies with CF_3I that were described in the Introduction, a two-week inhalation exposure range-finding study was performed (Kinkead et al., 1995). Four groups, each containing five male Fischer 344 rats, were exposed via nose only at

target concentrations of 12, 6, 3, or 0 (air-only control)% (vol/vol) CF_3I. Exposures were two hr/day, 5 days/wk, for a total of ten exposures. No deaths were observed, though lethargy and slight incoordination were noted in the high- and mid-concentration groups at the conclusion of each daily 2-h exposure. Mean body weight gains were depressed in the high-level group ($p<0.01$) at 7 days and 14 days, and in the mid-level group ($p<0.05$) at 7 days only. Serum thyroglobulin (HTG) and reverse T_3 (rT_3) values were significantly increased at all exposure levels. At necropsy, no gross lesions or differences in absolute or relative organ weights were noted. Histopathologic examination of the thyroid and parathyroids indicated no morphological abnormalities in CF_3I-exposed rats.

Failure of the high-concentration rats to gain weight during the two-week period, clinical signs of inactivity, and increases in serum HTG and rT_3 indicated that 12% CF_3I might be too stressful as a target concentration for the 90-day study. The mid-concentration group (6%) showed some minimal clinical signs of stress, such as transient weight-gain suppression and mild increases in serum HTG and rT_3 values. Increases in serum HTG and rT_3 were the only clinical findings noted in the low-concentration (3%) group. Given that the increases in serum HTG and rT_3 were not supported with microscopic findings in the thyroid and parathyroids, target concentrations chosen for the 90-day study were 8, 4, 2, and 0% CF_3I. The 8% concentration level was expected to produce clinical signs and, possibly, microscopic effects in the thyroid gland of CF_3I-exposed rats. The mid-concentration level (4%) was expected to produce minimal to no adverse effects in rats and the low-concentration level (2%) was expected to produce no adverse effects (i.e., a NOAEL).

Test Animals

Sixty male and 60 female Fischer 344 (F-344) rats were purchased from Charles River Breeding Laboratories, Raleigh, NC. The rats were six weeks of age upon arrival and nine weeks of age at the initiation of the 90-day exposure regimen. All rats were identified by tail tattoo and were subjected to a two-week quarantine period. Quality control testing consisted of monitoring body weights and examinations for ecto- and endoparasites. Randomly selected animals were sacrificed for gross pathologic examination and removal of liver and lung sections for histopathologic examination. Samples were also taken for bacteriology and virology assays. Results of quality control testing were negative. Water and feed (Purina Formulab #5002) were available *ad libitum,* except during exposure. Animal room temperatures were targeted at 21 to 25 °C, relative humidity at 40 to 60%, and the light/dark cycle was set at 12-hr intervals. Animals were single-housed in clear plastic cages with wood chip bedding (Betta-Chip, Northeastern Products Corp., Warrensburg, NY).

Exposure Regimen and Response Assessment

Fifteen male and 15 female F-344 rats were exposed 2 hr/day, 5 days/week, for up to 13 weeks (65 exposures over 90 days) to 0 (air-only), 2, 4, or 8% CF_3I. Prior to initiation of the CF_3I exposures, rats were acclimated to the nose-only chamber restraint system, breathing air only, 2 hr/day for one week. Five male and five female rats per group were necropsied after 30 days on study (20 exposures). Records were maintained for body weights (weekly), and signs of toxicity including mortality (twice daily). Euthanasia was via CO_2 inhalation overdose. At the 30- or 90-day sacrifice, gross pathology was performed and tissues were harvested for histopathologic examination. A list of tissues examined microscopically is shown in Appendix A. Wet tissue weights were determined on adrenals, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes, thymus, and thyroids (including parathyroids). Tissues were fixed in 10% neutral-buffered formalin, trimmed, and further processed via routine methods for H&E-stained, paraffin-embedded sections (Luna, 1968). Bouin's fixative was used to fix the testes and the epididymides.

As a suspected target organ, the thyroid glands were carefully processed by two necropsy technicians, according to a pre-determined protocol. Thyroids and parathyroids were removed with the trachea, fixed in 10% buffered formalin for 72 hours, then dissected free of the trachea with the aid of a zoom stereomicroscope (Olympus, Model BHS). Thyroid glands (isthmus intact) and attached parathyroid glands were then blotted and weighed to four decimal places (Mettler Model AE100 electronic balance). The thyroid glands were placed en-bloc into cassettes for paraffin embedding and sectioning.

Comparative measurement of thyroid follicular colloid was conducted on H&E-stained histologic thyroid sections (90-day sacrifice) using a Quantimet 570c Image Analysis System (Leica, Inc., Deerfield, IL). One section from each lobe was examined. Five digital images were obtained at 20X magnification in a linear fashion across the longest axis of the thyroid section. These images were collected in a manner that excluded any follicle that touched the exterior thyroid capsule and included all other follicles, both active and inactive. The image analysis algorithms involved thresholding the digital grey scale levels that corresponded to that of the follicular colloid. Filter-based elimination of random falsely-detected follicular colloid was confirmed manually and corrected as necessary. The resulting computer-based detected follicular colloid areas were measured by multiple parameters and expressed in square microns.

At both 30-day and 90-day animal sacrifices, blood was drawn immediately prior to kill from the vena cava for hematology and clinical chemistry assays. The hematological parameters included erythrocyte (RBC), leukocyte (WBC), differential leukocyte and platelet counts, hemoglobin (HGB), hematocrit (HCT), mean corpuscular hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC). Hematological parameters and absolute leukocyte differentials were determined according to established

procedures. Erythrocytes were enumerated on a Coulter counter (Coulter Electronics, Hialeah, FL). Serum was evaluated for albumin, alkaline phosphatase, alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), urea nitrogen, creatinine, calcium, glucose, potassium, phosphorus, sodium, total protein, magnesium, trigylcerides, cholesterol, thyroxine (T_4), thyroglobulin (HTG), triiodothyronine (T_3), reverse T_3 (rT_3), and thyroid stimulating hormone (TSH). Standard clinical chemistry evaluations were assayed on an Ektachem 250 (Eastman Kodak, Rochester, NY). Sera were processed according to the procedures in the Ektachem Operations manual. Thyroxine packs from DuPont Diagnostics were used for measuring the concentration of T_4 on an ACA®IV Discrete Clinical Analyzer. Assays for T_3, rT_3, TSH and HTG were performed using radioimmunoassay (RIA) kits and were carried out according to manufacturer's instructions. For all thyroid hormone or TSH measurements, assay kits were prepared for each animal sacrifice period (Study Day 30 or 90) using the same batch number and the same expiration date. Tracer (^{125}I) radioactivity was measured with a Packard Gamma Counter (Packard Instrument Co., Meriden,CT). Sources of the RIA kits and antiserum/antibody follow. For T_3, the RIA kit was purchased from Diagnostic Product Corporation (Los Angeles, CA), and canine T_3 antibody-coated tubes were used. Sera from the female rats killed at 30 days were not available for the measurement of T_3. For rT_3, the RIA kit was purchased from Wein Laboratories (Succasunna, NJ), and reverse T_3 antiserum raised in the rabbit was used. For TSH, the RIA kit was purchased from Amersham Corporation (Arlington Heights, IL); lyophilized rabbit anti-ratTSH serum and Amerlex-M second antibody (donkey anti-rabbit serum coated on to magnetized polymer particles containing sodium azide) were used. For HTG, the RIA kit was purchased from Wein Laboratories, and polystyrene tubes coated with three anti-human thyrogloulin mouse monoclonal antibodies were used followed by a fourth mouse monoclonal antibody (labelled with ^{125}I) directed against human thyroglobulin. Rat HTG and antiserum to rat HTG were not available commercially at the time of serum analysis.

Bone Marrow Toxicity/Mutagenicity Evaluation

Bone marrow cells were collected from the femur and smears were prepared from 5 rats/sex/group at both the 30-day and 90-day animal sacrifices to investigate the mutagenic potential of CF_3I via induction of micronuclei in bone marrow polychromatic erythrocytes. Two or three control rats/sex were administered a single dose of cyclophosphamide (7.5 mg/kg) intraperitoneally 24 hrs prior to sacrifice to serve as positive controls. Slides were stained by the Giemsa/May-Greenwald method and observed microscopically at 1000×. The frequency of micronucleated cells was evaluated by random observation of 1000 polychromatic erythrocytes (PCE) per sample. The ratio between PCE and normochromatic erythrocytes (NCE) was also determined by scoring approximately 1000 erythrocytes as an indicator of toxicity.

Statistical Analysis

Comparisons of mean body weights were performed using the multivariate analysis of covariance for repeated measures test (Rosner, 1990). A two-factorial (treatment and sex) analysis of variance with multivariate comparisons was used to analyze the hematology, clinical chemistry and organ weight data. The histopathology data were analyzed using Yates' corrected Chi-square (Zar, 1974). Chi-square analysis and one-way analysis (ANOVA) were used to evaluate data for the micronuclei induction and the PCE/NCE ratio changes.

SECTION III

RESULTS

Exposure System Analysis

The specified target concentrations of 8, 4, and 2% CF_3I were maintained during the daily 2-hr exposures. The exposure mean concentrations were maintained within ± 2% of the desired concentrations. Mean concentrations for each exposure, along with the lowest and highest daily mean concentrations are provided in Table 1. The daily mean relative humidity ranged between 47 and 52%, while the daily mean temperature ranged from 67 to 73 °F.

Table 1. CF_3I Concentrations Inhaled By Male And Female F-344 Rats

Target Concentration (%)	8.0	4.0	2.0
Mean Concentration (%)	8.05	4.03	2.02
Standard Error	0.01	>0.01	>0.01
Lowest Daily Mean (%)	7.94	3.95	1.99
Highest Daily Mean (%)	8.18	4.10	2.05
Mean Temperature (°F)	70.2	70.7	70.5
Mean Relative Humidity (%)	49.6	49.4	49.4

In-Life Observations

During the daily 2-hr exposures, rats of the 8% CF_3I group were highly active compared to air-only exposed rats; the 4% exposure group were moderately active and the 2% exposure group were mildly active. Since the rats were restrained in horizontal exposure tubes, the activities observed consisted of twisting or turning of the whole body, pushing backward from the front (exposure) end of the tube, and constant moving and/or pushing of the limbs against the tubular wall. (Note: An animal with increased activity continues to inhale the test material, due to the flow-past design of the nose-only exposure system.) For comparison, the rats of the control group were generally motionless and appeared to sleep throughout the exposure period. Following exposure, rats of the 8% group appeared lethargic.

Six male rats from the 2% CF_3I group died during the ninth day of exposure. A male rat from the 8% exposure group was found dead in its cage on the morning following 10 days of exposure. Another male rat of the 2% group died during the thirteenth exposure. Following the loss of six male rats on Exposure Day 9, the remaining male rats (all study groups) were placed into larger nose-only exposure tubes when their body weight reached 225 g. No additional changes in tube size were made once an animal was moved to a larger exposure tube. Because of the unexpected deaths, male rats from the 2% CF_3I group were not available for necropsy at the scheduled 30-day animal sacrifice.

A female rat assigned to the control group appeared moribund and was removed from the study during the pre-exposure acclimation period. This event resulted in a control group size of 14 female rats for the 90-day exposure regimen.

Mean body weights of the male and female rats of the 8% CF_3I group showed a slight decrease compared to control values through the first three weeks of the study. Mean body weights of the male group did not return to their pretreatment weight until 28 days into the study (Figure 1). Similarly, mean body weights of the 8% CF_3I female rats did not return to their pretreatment weight until 42 days into the study (Figure 2). The mean body weights of both the male and female high-concentration rats were statistically significantly ($p<0.01$) less than control values for the duration of the study. Mean body weights of the 4% CF_3I male rats were also less than control means ($p<0.01$) beginning on Study Day 14 and continuing through the remainder of the study. Mean body weights of the 4% CF_3I female rats differed ($p<0.05$) from the control means on Study Day 7 only. Mean body weight values for the 2% CF_3I rats did not differ from the body weight means of control rats.

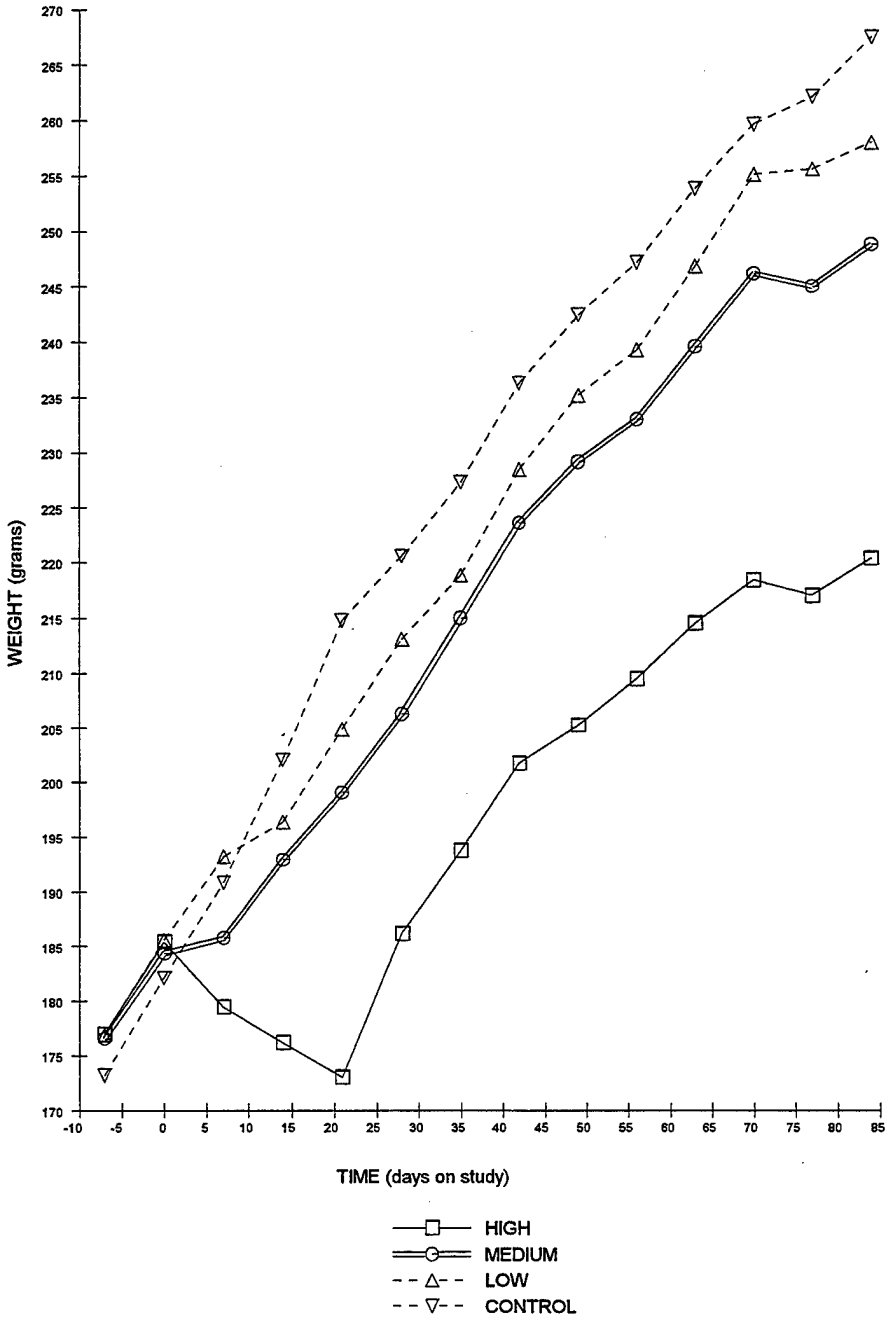


Figure 1. **Mean Body Weights of Male F-344 Rats Exposed to CF_3I Vapor for 90 Days In Nose-Only Chambers**

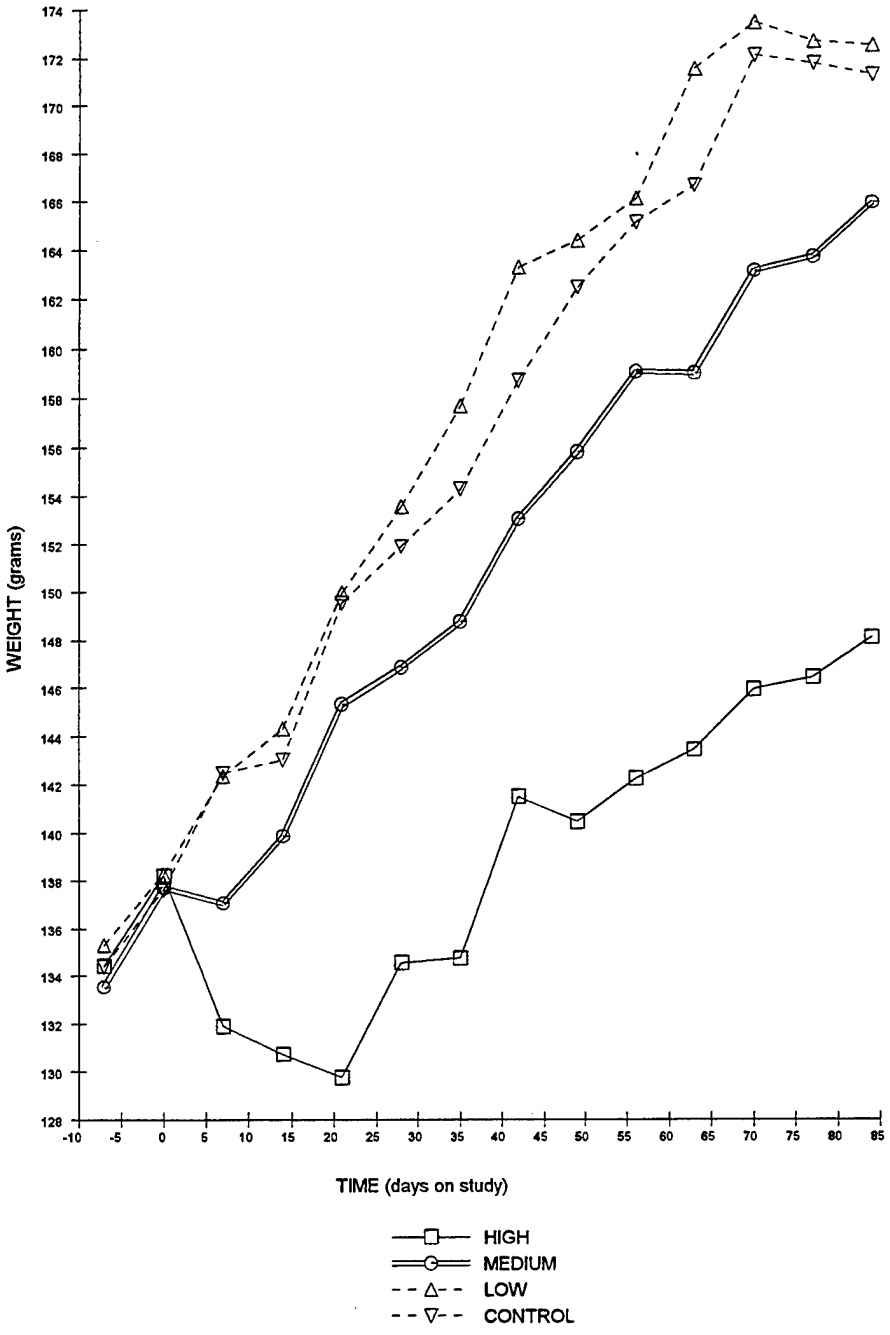


Figure 2. **Mean Body Weights of Female F-344 Rats Exposed to CF_3I Vapor for 90 Days in Nose-Only Chambers.**

Hematology

30 Days. The mean values of hemoglobin concentration, red blood cell count, and lymphocyte percentage were statistically significantly decreased in the 8% CF_3I male rats compared to control male rat values; neutrophil percentage was increased (Table 2). Mean lymphocyte percentages were also less than the control means in the 4% CF_3I male rat group and the 8% female rat group (Table 3).

Table 2. Blood Hematology Values[a] of Male F-344 Rats following 30 Days of Treatment with CF_3I

	Control	Low	Medium	High
WBC (10^3)	7.12 ± 0.49	-	7.98 ± 0.38	8.68 ± 0.46
RBC (10^6)	8.61 ± 0.06	-	8.35 ± 0.11	8.01 ± 0.16[c]
HGB (g/dL)	15.7 ± 0.09	-	15.4 ± 0.17	14.8 ± 0.27[c]
HCT (%)	44.1 ± 0.08	-	43.4 ± 0.43	42.2 ± 0.77
MCV (fL)	51.1 ± 0.34	-	51.8 ± 0.26	52.7 ± 0.52
MCHC (g/dL)	35.6 ± 0.20	-	35.4 ± 0.16	35.0 ± 0.20
Platelets (10^3)	679 ± 23	-	659 ± 8.4	781 ± 55
Neutrophils (%)	12.4 ± 2.3	-	25.0 ± 2.6	30.4 ± 4.8[b]
Lymphocytes (%)	82.6 ± 3.0	-	71.2 ± 2.0[c]	63.6 ± 4.1[b]
Monocytes (%)	2.00 ± 0.71	-	3.80 ± 1.3	5.40 ± 1.9
Eosinophils (%)	1.00 ± 0.77	-	0.00 ± 0.00	0.60 ± 0.40
Basophils (%)	0.00 ± 0.00	-	0.00 ± 0.00	0.00 ± .00

[a]Mean ± SEM, N=5.
[b]Significantly different from control, p<0.01.
[c]Significantly different from control, p<0.05.

Table 3. Blood Hematology Values[a] of Female F-344 Rats following 30 Days of Treatment with CF_3I

	Control	Low	Medium	High
WBC (10^3)	7.14 ± 0.58	7.34 ± 0.50	6.54 ± 0.36	6.32 ± 0.52
RBC (10^6)	7.88 ± 0.06	7.96 ± 0.08	7.79 ± 0.14	7.78 ± 0.11
HGB (g/dL)	15.1 ± 0.11	15.3 ± 0.17	15.1 ± 0.14	15.0 ± 0.14
HCT (%)	42.2 ± 0.38	42.5 ± 0.57	42.2 ± 0.62	42.6 ± 0.44
MCV (fL)	53.4 ± 0.21	53.3 ± 0.49	54.1 ± 0.71	54.7 ± 0.95
MCHC (g/dL)	35.8 ± 0.07	35.9 ± 0.13	35.7 ± 0.34	35.3 ± 0.26
Platelets (10^3)	658 ± 18	633 ± 21	653 ± 18	715 ± 38
Neutrophils (%)	13.8 ± 2.6	12.6 ± 1.9	13.0 ± 2.0	25.8 ± 2.6
Lymphocytes (%)	81.6 ± 1.9	78.8 ± 2.2	81.4 ± 1.8	70.4 ± 2.5[b]
Monocytes (%)	3.20 ± 0.58	6.60 ± 1.2	3.20 ± 0.37	3.00 ± 0.45
Eosinophils (%)	1.40 ± 0.98	1.80 ± 0.49	2.20 ± 0.37	0.80 ± 0.49
Basophils (%)	0.00 ± 0.00	0.20 ± 0.20	0.00 ± 0.00	0.00 ± 0.00

[a]Mean ± SEM, N=5.
[b]Significantly different from control, p<0.01.

90 Days. Mean red blood cell count and lymphocyte percentage in the 8% CF_3I-exposed male rats remained statistically significantly less than control values (Table 4). Mean lymphocyte percentages were also decreased in the 8% female rat group (Table 5). The observed decreases in mean hematologic indices due to CF_3I exposure were mild (< 10%) in magnitude.

Table 4. Blood Hematology Values[a] of Male F-344 Rats following 90 Days of Treatment with CF_3I

	Control	Low	Medium	High
WBC (10^3)	6.61 ± 0.39	7.12 ± 0.43	7.00 ± 0.34	5.45 ± 0.33
RBC (10^6)	9.17 ± 0.19	8.98 ± 0.18	9.39 ± 0.13	8.92 ± 0.14[c]
HGB (g/dL)	16.2 ± 0.34	15.8 ± 0.34	16.5 ± 0.23	15.8 ± 0.27
HCT (%)	51.7 ± 1.1	50.6 ± 1.0	53.0 ± 1.2	50.2 ± 0.83
MCV (fL)	56.4 ± 0.15	56.3 ± 0.40	56.4 ± 0.70	56.3 ± 0.25
MCHC (g/dL)	31.3 ± 0.16	31.3 ± 0.17	31.1 ± 0.31	31.5 ± 0.15
Platelets (10^3)	589 ± 16	602 ± 28	577 ± 8.7	651 ± 18
Neutrophils (%)	21.5 ± 1.5	21.9 ± 1.7	23.5 ± 1.3	26.4 ± 1.3
Lymphocytes (%)	72.7 ± 1.5	72.1 ± 1.5	70.6 ± 1.3	67.8 ± 1.2[b]
Monocytes (%)	2.59 ± 0.16	3.19 ± 0.29	3.07 ± 0.14	3.06 ± 0.24
Eosinophils (%)	1.01 ± 0.09	0.90 ± 0.06	0.94 ± 0.05	0.84 ± 0.10
Basophils (%)	0.77 ± 0.06	0.61 ± 0.07	0.63 ± 0.07	0.60 ± 0.07

[a]Mean ± SEM.
[b]Significantly different from control, $p<0.01$.
[c]Significantly different from control, $p<0.05$.

Table 5. Blood Hematology Values[a] of Female F-344 Rats following 90 Days of Treatment with CF_3I

	Control	Low	Medium	High
WBC (10^3)	6.93 ± 0.42	7.01 ± 0.25	6.47 ± 0.31	5.45 ± 0.22
RBC (10^6)	8.28 ± 0.16	8.33 ± 0.12	8.11 ± 0.14	8.59 ± 0.08
HGB (g/dL)	15.4 ± 0.30	15.7 ± 0.19	15.0 ± 0.29	16.0 ± 0.17
HCT (%)	48.6 ± 1.05	48.7 ± 0.66	47.3 ± 0.81	50.3 ± 0.39
MCV (fL)	58.6 ± 0.24	58.5 ± 0.40	58.4 ± 0.17	54.7 ± 4.0
MCHC (g/dL)	31.6 ± 0.15	32.2 ± 0.20	31.8 ± 0.12	29.9 ± 1.8
Platelets (10^3)	629 ± 17	612 ± 19	582 ± 16	580 ± 67
Neutrophils (%)	16.8 ± 1.1	16.7 ± 1.1	19.6 ± 1.6	20.1 ± 0.99
Lymphocytes (%)	76.7 ± 1.3	77.4 ± 1.2	74.4 ± 1.8	74.2 ± 1.3[c]
Monocytes (%)	3.19 ± 0.34	3.06 ± 0.21	3.30 ± 0.16	2.81 ± 0.24
Eosinophils (%)	0.89 ± 0.09	1.00 ± 0.07	0.80 ± 0.06	0.95 ± 0.10
Basophils (%)	0.90 ± 0.06	0.62 ± 0.06	0.57 ± 0.08	0.66 ± 0.11

[a]Mean ± SEM.
[b]Significantly different from control, $p<0.01$.
[c]Significantly different from control, $p<0.05$.

Serum Chemistry

30 Days. Mean calcium and glucose levels were decreased, and ALT and globulin levels were statistically significantly increased compared to control values in the 8% CF_3I male and female rat groups (Tables 6 & 7). The mean triglycerides value was decreased in the 8% male rats only. A number of statistically significant treatment- and/or concentration-related effects were observed in several thyroid hormone values (Tables 6 & 7). Mean thyroglobulin (HTG) levels were increased at all CF_3I exposure levels in female rats and at the 8% CF_3I level

Table 6. Mean Values[a] of Serum Chemistry Parameters for Male F-344 Rats ollowing 30 Days of Treatment with CF_3I

	Control	Low	Medium	High
UN (mg/dL)	17.8 ± 0.37	-	17.2 ±0.58	17.0 ± 0.32
Creatinine (mg/dL)	0.40 ± 0.00	-	0.38 ± 0.02	0.40 ± 0.00
Calcium (mg/dL)	11.9 ± 0.12	-	11.7 ± 0.12	11.5 ± 0.11[c]
Phosphorus (mg/dL)	9.52 ± 0.59	-	9.86 ± 0.30	9.60 ± 0.14
Total Protein (g/dL)	6.82 ± 0.10	-	6.90 ± 0.05	6.86 ± 0.11
AST (IU/L)	106 ± 3.4	-	111 ± 7.9	113 ± 5.7
ALT (IU/L)	56.4 ± 2.4	-	57.6 ± 2.4	66.4 ± 3.0[c]
Alkaline phosphatase	292 ± 12	-	312 ± 13	281 ± 11
Albumin (g/dL)	3.68 ± 0.10	-	3.74 ± 0.05	3.66 ± 0.05
Globulin	3.12 ± 0.04	-	3.16 ± 0.02	3.2 ± 0.05[c]
A/G Ratio	1.18 ± 0.04	-	1.18 ± 0.02	1.14 ± 0.02
Glucose (mg/dL)	178 ± 6.7	-	163 ± 5.4	153 ± 6.7[b]
Sodium (mmol/L)	150 ± 0.37	-	148 ± 0.32	147 ± 0.37
Triglycerides (mg/dL)	112 ± 14	-	114 ± 4.2	76.2 ± 7.8[c]
Magnesium (mg/dL)	3.06 ± 0.22	-	3.10 ± 0.11	3.28 ± 0.15
Potassium (mmol/L)	4.98 ± 0.07	-	5.10 ± 0.06	5.24 ± 0.14
Cholesterol (mg/dL)	51.0 ± 0.00	-	53.0 ± 0.00	56.0 ± 2.5
Thyroglobulin (ng/mL)	1.13 ± 0.04	-	1.25 ± 0.04	1.65 ± 0.06[b]
T_3 (ng/mL)	320 ± 9.54	-	166 ± 4.20[b]	157 ± 8.15[b]
T_4 (mg/dL)	3.78 ± 0.3	-	5.22 ± 0.1[c]	4.62 ± 0.3[c]
rT_3 (ng/dL)	5.12 ± 0.17	-	5.41 ± 0.22	6.75 ± 0.42[b]
TSH (ng/mL)	3.34 ± 0.05	-	3.74 ± 0.13	4.70 ± 0.15[b]

[a]Mean ± SEM, N=5.
[b]Significantly different from control, p<0.01.
[c]Significantly different from control, p<0.05.

in male rats when compared to respective female and male rat control values. Mean thyroxine (T_4) levels were increased in all CF_3I exposure groups. Mean triiodothyronine (T_3) levels were decreased in male rats of the 8 and 4% CF_3I groups; neither the 2% male rats nor the female rats were assayed. Mean reverse T_3 (rT_3) levels were increased in the 8% male rats and the 4 and 8% female rats. Mean thyroid stimulating hormone (TSH) concentrations were elevated in all CF_3I-exposed female rat groups, as well as in the 8% male rats.

Table 7. **Mean Values[a] of Serum Chemistry Parameters for Female F-344 Rats following 30 Days of Treatment with CF_3I**

	Control	Low	Medium	High
UN (mg/dL)	17.0 ± 0.45	17.8 ± 1.3	18.2 ± 0.49	19.2 ± 0.86
Creatinine (mg/dL)	0.32 ± 0.02	0.36 ± 0.02	0.30 ± 0.00	0.30 ± 0.00
Calcium (mg/dL)	10.9 ± 0.11	11.1 ± 0.09	10.8 ± 0.07	10.5 ± 0.07[c]
Phosphorus (mg/dL)	9.48 ± 0.39	10.4 ± 0.12	10.1 ± 0.27	9.74 ± 0.19
Total Protein (g/dL)	6.16 ± 0.07	6.08 ± 0.09[c]	6.30 ± 0.05	6.52 ± 0.16
AST (IU/L)	114 ± 3.7	105 ± 4.2	108 ± 1.6	119 ± 8.3
ALT (IU/L)	57.8 ± 2.7	49.4 ± 2.2[c]	54.4 ± 1.9	77.4 ± 9.5[c]
Alkaline phosphatase	245 ± 5.6	273 ± 15	274 ± 14	273 ± 12
Albumin (g/dL)	3.28 ± 0.04	3.22 ± 0.07	3.30 ± 0.04	3.34 ± 0.07
Globulin	2.90 ± 0.03	2.86 ± 0.02	3.00 ± 0.04	3.18 ± 0.07[c]
A/G Ratio	1.14 ± 0.02	1.12 ± 0.02	1.10 ± 0.03	1.06 ± 0.02
Glucose (mg/dL)	155 ± 4.4	156 ± 11	141 ± 8.0	129 ± 6.4[b]
Sodium (mmol/L)	148 ± 0.51	146 ± 0.51	147 ± 0.37	149 ± 0.58
Triglycerides (mg/dL)	40.6 ± 2.8	45.6 ± 5.0	41.8 ± 4.5	48.2 ± 11
Magnesium (mg/dL)	2.74 ± 0.09	2.86 ± 0.18	3.00 ± 0.14	2.92 ± 0.14
Potassium (mmol/L)	5.82 ± 0.31	5.88 ± 0.21	5.62 ± 0.27	5.30 ± 0.16
Cholesterol (mg/dL)	53.6 ± 0.81	56.5 ± 4.5	56.0 ± 1.3	65.8 ± 3.7
Thyroglobulin (ng/mL)	0.37 ± 0.02	0.52 ± 0.02[b]	0.78 ± 0.03[b]	0.84 ± 0.02[b]
T_4 (mg/dL)	2.56 ± 0.2	3.86 ± 0.1[c]	4.28 ± 0.1[c]	3.52 ± 0.1[c]
rT_3 (ng/dL)	3.63 ± 0.02	4.03 ± 0.13	4.27 ± 0.18[b]	5.42 ± 0.08[b]
TSH (ng/mL)	4.54 ± 0.16	6.53 ± 0.24[b]	6.89 ± 0.16[b]	7.20 ± 0.24[b]

[a]Mean ± SEM, N=5.
[b]Significantly different from control, $p<0.01$.
[c]Significantly different from control, $p<0.05$.

90 Days. Compared to control means, statistically significant decreases in calcium and ALT values were observed in both male and female rats exposed to 8% CF_3I (Tables 8 & 9). Mean glucose was decreased in the 8% female rats, and mean trigylcerides were decreased in the 8% male rats. As observed in the 30-day animal sacrifice, a number of statistically significant treatment- and/or concentration-related effects were observed in several thyroid hormone values (Tables 8 & 9). Increases in mean HTG, T_4 and TSH, and decreases in mean T_3 were observed in all CF_3I-exposed male and female rat groups, except for HTG concentration in the 2% female rats. Mean rT_3 values were increased in both male and female rats of the 4 and 8% CF_3I groups.

Table 8. Mean Values[a] of Serum Chemistry Parameters for Male F-344 Rats following 90 Days of Treatment with CF_3I

	Control	Low	Medium	High
UN (mg/dL)	20.7 ± 1.2	21.0 ± 1.7	19.7 ± 0.72	20.4 ± 0.60
Creatinine (mg/dL)	0.43 ± 0.02	0.44 ± 0.03	0.42 ± 0.01	0.41 ± 0.01
Calcium (mg/dL)	11.1 ± 0.15	10.9 ± 0.12	11.0 ± 0.24	10.9 ± 0.13[c]
Phosphorus (mg/dL)	9.22 ± 0.28	9.06 ± 0.36	9.39 ± 0.22	9.52 ± 0.32
Total Protein (g/dL)	6.79 ± 0.06	6.66 ± 0.11	6.52 ± 0.07	6.78 ± 0.09
AST (IU/L)	114 ± 7.6	106 ± 5.2	107 ± 6.1	105 ± 8.5
ALT (IU/L)	66.4 ± 4.8	65.8 ± 2.3	68.2 ± 2.9	62.7 ± 2.3[c]
Alkaline phosphatase	268 ± 11	285 ± 6.6	272 ± 9.8	257 ± 7.7
Albumin (g/dL)	3.83 ± 0.06	3.73 ± 0.10	3.70 ± 0.06	3.91 ± 0.08
Globulin	2.93 ± 0.04	2.84 ± 0.06	2.82 ± 0.04	2.84 ± 0.02
A/G Ratio	1.31 ± 0.03	1.32 ± 0.06	1.31 ± 0.02	1.36 ± 0.03
Glucose (mg/dL)	148 ± 3.9	150 ± 6.0	162 ± 6.5	137 ± 3.0
Sodium (mmol/L)	151 ± 1.5	155 ± 2.2	150 ± 1.2	154 ± 2.0
Triglycerides (mg/dL)	117 ± 19	133 ± 17	95.5 ± 7.5	74.8 ± 7.8[c]
Magnesium (mg/dL)	2.88 ± 0.10	2.76 ± 0.10	2.85 ± 0.10	2.90 ± 0.09
Potassium (mmol/L)	5.20 ± 0.09	5.29 ± 0.14	5.32 ± 0.09	5.49 ± 0.15
Cholesterol (mg/dL)	55.2 ± 1.9	53.3 ± 1.5	47.5 ± 7.0	56.8 ± 1.5
Thyroglobulin (ng/mL)	0.27 ±<0.01	0.46 ± 0.01[b]	0.60 ± 0.02[b]	1.11 ± 0.02[b]
T_3 (ng/mL)	271 ± 7.6	192 ± 5.5[b]	176 ± 7.2[b]	134 ± 4.8[b]
T_4 (mg/dL)	2.84 ± 0.2	3.53 ± 0.1[c]	3.10 ± 0.2[c]	3.09 ± 0.2[c]
rT_3 (ng/dL)	6.66 ± 0.1	6.96 ± 0.2	8.91 ± 0.2[b]	9.66 ± 0.3[b]
TSH (ng/mL)	3.21 ± 0.1	4.68 ± 0.1[b]	6.14 ± 0.2[b]	8.14 ± 0.2[b]

[a]Mean ± SEM.
[b]Significantly different from control, $p<0.01$.
[c]Significantly different from control, $p<0.05$.

Table 9. Mean Values[a] of Serum Chemistry Parameters for Female F-344 Rats Following 90 Days of Treatment with CF_3I

	Control	Low	Medium	High
UN (mg/dL)	21.0 ± 1.0	18.9 ± 2.3	21.2 ± 1.2	23.9 ± 1.2
Creatinine (mg/dL)	0.44 ± 0.04	0.46 ± 0.02	0.44 ± 0.02	0.42 ± 0.02
Calcium (mg/dL)	10.8 ± 0.23	10.6 ± 0.15	10.6 ± 0.19	10.4 ± 0.14[c]
Phosphorus (mg/dL)	8.74 ± 0.21	8.41 ± 0.21	8.61 ± 0.17	9.03 ± 0.34
Total Protein (g/dL)	6.47 ± 0.11	6.13 ± 0.06[c]	6.31 ± 0.09	6.43 ± 0.10
AST (IU/L)	154 ± 45	140 ± 31	149 ± 20	141 ± 15
ALT (IU/L)	60.7 ± 4.8	57.3 ± 2.1	67.0 ± 8.8	52.5 ± 1.8[c]
Alkaline phosphatase	265 ± 16	269 ± 11	278 ± 6.3	275 ± 7.2
Albumin (g/dL)	3.62 ± 0.10	3.42 ± 0.05	3.48 ± 0.09	3.58 ± 0.10
Globulin	2.81 ± 0.04	2.73 ± 0.03	2.83 ± 0.03	2.85 ± 0.03
A/G Ratio	1.28 ± 0.04	1.26 ± 0.02	1.24 ± 0.04	1.27 ± 0.03
Glucose (mg/dL)	136 ± 7.5	135 ± 5.5	131 ± 3.5	128 ± 4.1[b]
Sodium (mmol/L)	155 ± 3.4	150 ± 1.9	152 ± 2.2	151 ± 2.5
Triglycerides (mg/dL)	56.4 ± 5.9	54.7 ± 6.1	50.8 ± 4.4	46.6 ± 3.4
Magnesium (mg/dL)	2.68 ± 0.11	2.69 ± 0.07	2.73 ± 0.08	2.74 ± 0.09
Potassium (mmol/L)	5.82 ± 0.14	5.53 ± 0.12	5.78 ± 0.19	5.90 ± 0.16
Cholesterol (mg/dL)	67.2 ± 2.6	57.2 ± 1.8	57.6 ± 1.2	56.7 ± 2.4
Thyroglobulin (ng/mL)	0.44 ± 0.01	0.51 ± 0.01	0.76 ± 0.02[b]	1.10 ± 0.04[b]
T_3 (ng/mL)	274 ± 8.5	190 ± 6.3[b]	167 ± 3.8[b]	123 ± 3.0[b]
T_4 (mg/dL)	2.82 ± 0.1	4.20 ± 0.2[c]	4.09 ± 0.2[c]	3.92 ± 0.2[c]
rT_3 (ng/dL)	6.72 ± 0.2	7.12 ± 0.01	8.64 ± 0.2[b]	10.17 ± 0.4[b]
TSH (ng/mL)	4.36 ± 0.1	5.73 ± 0.2[b]	7.77 ± 0.1[b]	9.38 ± 0.2[b]

[a]Mean ± SEM.
[b]Significantly different from control, $p<0.01$.
[c]Significantly different from control, $p<0.05$.

Organ Weights

30 Days. The weights of several organs were affected by CF_3I exposure. Statistically significant concentration-related decreases in absolute and relative (to body weight) mean thymic weights occurred in male and female rats exposed to 4 or 8% CF_3I (Tables 10 & 11). Mean testes weights of the 8% CF_3I-exposed male rats were decreased approximately 30% compared to control males. The means of relative thyroid weights were greater than control

Table 10. Absolute (g) and Relative Organ Weights[a] of Male F-344 Rats Treated with CF_3I for 30 Days

Organs	Control	Low	Medium	High
Body Weight	218.48 ± 8.21	---	213.46 ± 4.99	187.24 ± 7.39[c]
Brain	1.70 ± 0.02	---	1.71 ± 0.01[c]	1.65 ± 0.03[c]
Ratio[b]	0.78 ± 0.03	---	0.80 ± 0.02	0.89 ± 0.03[d]
Liver	7.37 ± 0.41	---	7.72 ± 0.31	6.94 ± 0.39
Ratio	3.37 ± 0.08	---	3.61 ± 0.07	3.70 ± 0.11[d]
Kidneys	1.81 ± 0.18	---	1.63 ± 0.05	1.46 ± 0.09[c]
Ratio	0.83 ± 0.10	---	0.76 ± 0.01	0.78 ± 0.02
Spleen	0.43 ± 0.02	---	0.39 ± 0.01[d]	0.35 ± 0.02[d]
Ratio	0.19 ± 0.01	---	0.18 ±<0.01	0.19 ±<0.01
Thymus	0.23 ± 0.02	---	0.18 ± 0.01[d]	0.19 ± 0.02[d]
Ratio	0.105 ± 0.01	---	0.084 ± 0.01[c]	0.099 ± 0.01[c]
Heart	0.72 ± 0.04	---	0.67 ± 0.02	0.67 ± 0.03
Ratio	0.33 ± 0.01	---	0.32 ± 0.01	0.36 ± 0.01
Adrenal Gland	0.05 ± 0.01	---	0.04 ± 0.01	0.05 ± 0.01
Ratio	0.02 ± <0.01	---	0.02 ± <0.01	0.03 ± <0.01
Lungs	1.38 ± 0.04	---	1.19 ± 0.06	1.16 ± 0.09[d]
Ratio	0.63 ± 0.01	---	0.56 ± 0.02	0.62 ± 0.03
Thyroid[e]	17.00 ± <0.01	---	16.20 ± <0.01	14.25 ± <0.01[f]
Ratio	0.0076 ± <0.01	---	0.0076 ± <0.01	0.0078 ± <0.01[cf]
Testes	2.53 ± 0.07	---	2.34 ± 0.08	1.63 ± 0.07[d]
Ratio	1.16 ± 0.02	---	1.10 ± 0.03	0.87 ± 0.02[d]

[a]Mean ± SEM, N=5.
[b]Organ weight/body weight x 100.
[c]Significantly different from control, $p<0.05$.
[d]Significantly different from control, $p<0.01$.
[e]Expressed as mg.
[f]N=4.

values in the 8% and 4% (female rats only) CF_3I groups. The relative mean weights of liver and brain were increased mildly in male and female rats of the high-exposure CF_3I group. Relative weight values for the kidneys, spleen, heart, adrenals, lungs and ovaries (female rats) of CF_3I-exposed animals did not differ from control values.

Table 11. Absolute (g) and Relative Organ Weights[a] of Female F-344 Rats Treated with CF_3I for 30 Days

Organs	Control	Low	Medium	High
Body Weight	152.47 ± 2.11	147.74 ± 3.78	150.16 ± 1.82	138.16 ± 2.74[c]
Brain	1.72 ± 0.03	1.64 ± 0.04	1.65 ± 0.02	1.60 ± 0.01[c]
Ratio[b]	1.12 ± 0.02	1.11 ± 0.02	1.09 ± 0.02	1.16 ± 0.03[d]
Liver	5.14 ± 0.11	4.76 ± 0.19	5.16 ± 0.14	5.14 ± 0.14
Ratio	3.35 ± 0.07	3.23 ± 0.05	3.42 ± 0.08	3.72 ± 0.07[d]
Kidneys	1.12 ± 0.02	1.16 ± 0.03	1.19 ± 0.03	1.11 ± 0.02[c]
Ratio	0.79 ± 0.01	0.78 ± 0.01	0.79 ± 0.02	0.81 ± 0.03
Spleen	0.39 ± 0.01	0.34 ± 0.02	0.32 ± 0.02[d]	0.30 ± 0.01[d]
Ratio	0.25 ± 0.01	0.23 ± 0.01	0.21 ± 0.01	0.21 ± 0.01
Thymus	0.23 ± 0.02	0.20 ± 0.03[c]	0.17 ± 0.02[d]	0.15 ± 0.01[d]
Ratio	0.15 ± 0.01	0.13 ± 0.02	0.11 ± 0.02[c]	0.11 ± 0.01[c]
Heart	0.56 ± 0.01	0.54 ± 0.02	0.54 ± 0.01	0.56 ± 0.01
Ratio	0.37 ± 0.01	0.36 ± 0.01	0.36 ± 0.01	0.40 ± 0.01
Adrenal Gland	0.09 ± 0.01	0.10 ± 0.01	0.06 ± 0.01	0.08 ± 0.01
Ratio	0.06 ± 0.01	0.07 ± 0.01	0.04 ± 0.01	0.06 ± 0.01
Lungs	1.10 ± 0.04	1.05 ± 0.05	1.08 ± 0.03	1.08 ± 0.04
Ratio	0.72 ± 0.03	0.71 ± 0.02	0.72 ± 0.01	0.78 ± 0.03
Thyroid[e]	11.60 ± <0.01	11.00 ± <0.01	14.40 ± <0.01	11.80 ± <0.01
Ratio	0.0074 ± <0.01	0.0074 ± <0.01	0.0096 ± <0.01[c]	0.0084 ± <0.01[c]
Ovaries	0.11 ± 0.02	0.11 ± 0.01	0.08 ± 0.01[c]	0.08 ± 0.01[c]
Ratio	0.07 ± 0.01	0.08 ± 0.01	0.05 ± 0.01	0.06 ± 0.01

[a]Mean ± SEM, N=5.
[b]Organ weight/body weight x 100.
[c]Significantly different from control, $p<0.05$.
[d]Significantly different from control, $p<0.01$.
[e]Expressed as mg.

90 Days. Relative mean thymic weights of CF_3I-exposed female rats (2, 4 and 8% groups) and male rats (4 and 8% groups) were statistically significantly lower than the control means (Tables 12 and 13). Mean testes weights of the 8% CF_3I-exposed male rats were decreased compared to control males. The relative mean thyroid weights of male CF_3I-exposed

Table 12. Absolute (g) and Relative Organ Weights[a] of Female F-344 Rats Treated with CF_3I for 90 Days

Organs	Control	Low	Medium	High
Body Weight	170.61 ± 3.51	172.22 ± 2.53	164.95 ± 2.28	147.43 ± 1.91[c]
Brain	1.81 ± 0.03	1.77 ± 0.03	1.71 ± 0.05[c]	1.68 ± 0.02[c]
Ratio[b]	1.07 ± 0.03	1.04 ± 0.02	1.04 ± 0.02	1.14 ± 0.02[d]
Liver	5.32 ± 0.13	5.40 ± 0.16	5.28 ± 0.22	4.81 ± 0.20
Ratio	3.11 ± 0.03	3.16 ± 0.09	3.19 ± 0.09	3.26 ± 0.12[d]
Kidneys	1.32 ± 0.03	1.28 ± 0.02	1.32 ± 0.07	1.22 ± 0.02[c]
Ratio	0.78 ± 0.01	0.75 ± 0.01	0.80 ± 0.04	0.83 ± 0.01
Spleen	0.46 ± 0.02	0.40 ± 0.01	0.39 ± 0.02[d]	0.33 ± 0.01[d]
Ratio	0.27 ± 0.01	0.24 ± 0.01	0.24 ± 0.01	0.23 ± 0.01
Thymus	0.22 ± 0.02	0.18 ± 0.01[c]	0.18 ± 0.01[d]	0.15 ± 0.01[d]
Ratio	0.131 ± 0.01	0.107 ± 0.01[c]	0.108 ± 0.01[c]	0.103 ± 0.01[c]
Heart	0.64 ± 0.03	0.60 ± 0.01	0.61 ± 0.02	0.57 ± 0.02
Ratio	0.37 ± 0.02	0.35 ± 0.01	0.37 ± 0.01	0.38 ± 0.01
Adrenal Gland	0.12 ± 0.02	0.07 ± 0.01	0.08 ± 0.01	0.07 ± 0.01
Ratio	0.07 ± 0.01	0.04 ± 0.00	0.05 ± 0.01	0.05 ± 0.01
Lungs	1.30 ± 0.05	1.24 ± 0.03	1.22 ± 0.04	1.13 ± 0.03[d]
Ratio	0.76 ± 0.02	0.73 ± 0.01	0.74 ± 0.02	0.77 ± 0.03
Thyroid[e]	16.00 ± <0.01	15.20 ± <0.01	15.70 ± <0.01	16.80 ± <0.01
Ratio	0.0091 ± <0.01	0.0089 ± <0.01	0.0095 ± <0.01	0.00112 ± <0.01[d]
Ovaries	0.16 ± 0.02	0.11 ± 0.01	0.10 ± 0.01[c]	0.10 ± 0.01[c]
Ratio	0.10 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.07 ± 0.01

[a]Mean ± SEM, N=10.
[b]Organ weight/body weight x 100.
[c]Significantly different from control, $p<0.05$.
[d]Significantly different from control, $p<0.01$.
[e]Expressed as mg.

rats (2, 4 and 8% groups) and female rats (8% only) were increased compared to respective control values. The relative mean weights of liver and brain were increased mildly in male and female rats of the high-exposure CF_3I group. Relative weight values for the kidneys, spleen, heart, adrenals, lungs and ovaries (female rats) of CF_3I-exposed animals did not differ from control values.

Table 13. Absolute (g) and Relative Organ Weights[a] of Male F-344 Rats Treated with CF_3I for 90 Days

Organs	Control[e]	Low[f]	Medium[g]	High[e]
Body Weight	269.84 ± 10.25	261.56 ± 11.62	250.32 ± 7.91	222.77 ± 3.44[c]
Brain	1.91 ± 0.03	1.83 ± 0.05	1.78 ± 0.04[c]	1.82 ± 0.06[c]
Ratio[b]	0.71 ± 0.03	0.71 ± 0.03	0.72 ± 0.02	0.82 ± 0.02[d]
Liver	8.78 ± 0.40	8.53 ± 0.44	8.23 ± 0.34	7.40 ± 0.19
Ratio	3.25 ± 0.06	3.26 ± 0.05	3.28 ± 0.05	3.32 ± 0.05[d]
Kidneys	1.95 ± 0.07	1.82 ± 0.08	1.81 ± 0.06	1.66 ± 0.05[c]
Ratio	0.72 ± 0.02	0.70 ± 0.01	0.72 ± 0.01	0.74 ± 0.01
Spleen	0.58 ± 0.03	0.70 ± 0.18	0.48 ± 0.01[d]	0.44 ± 0.03[d]
Ratio	0.21 ± 0.01	0.26 ± 0.06	0.19 ± 0.01	0.20 ± 0.01
Thymus	0.25 ± 0.02	0.22 ± 0.02[c]	0.21 ± 0.01[d]	0.18 ± 0.02[d]
Ratio	0.087± 0.01	0.086 ± 0.01	0.083 ± <0.01[c]	0.081 ± 0.01[c]
Heart	0.87 ± 0.03	0.85 ± 0.04	0.89 ± 0.10	0.77 ± 0.04
Ratio	0.32 ± 0.01	0.33 ± 0.02	0.36 ± 0.05	0.35 ± 0.02
Adrenal Gland	0.11 ± 0.02	0.10 ± 0.03	0.07 ± 0.01	0.09 ± 0.02
Ratio	0.04 ± 0.01	0.04 ± 0.01	0.03 ± <0.01	0.04 ± 0.01
Lungs	1.71 ± 0.06	1.62 ± 0.05	1.52 ± 0.07	1.42 ± 0.05[d]
Ratio	0.63 ± 0.01	0.63 ± 0.05	0.61 ± 0.02	0.64 ± 0.02
Thyroid[h]	18.30 ± <0.01	20.12 ± <0.01	18.70 ± <0.01	17.22 ± <0.01
Ratio	0.0067 ± <0.01	0.0080 ± <0.01[c]	0.0076 ± <0.01[c]	0.0078 ± <0.01[c]
Testes	2.85 ± 0.04	2.59 ± 0.12	2.52 ± 0.08	2.06 ± 0.14[d]
Ratio	1.07 ± 0.03	1.00 ± 0.06	1.01 ± 0.02	0.92 ± 0.06[d]

[a]Mean ± SEM.
[b]Organ weight/body weight x 100.
[c]Significantly different from control, $p<0.05$.
[d]Significantly different from control, $p<0.01$.
[e]N=9.
[f]N=8.
[g]N=10.
[h]Expressed as mg.

Bone Marrow Micronuclei Induction

30 Days. The results of the micronuclei examination of bone marrow polychromatic erythrocytes of male and female rats indicate that CF_3I at concentrations of 4 and 8% increased the micronuclei frequency in male rats by 2.7- and 3.9-fold, respectively, and in female rats, 3.5- and 4.9-fold, respectively (Table 14). Rats administered the positive control agent, cyclophosphamide, increased micronuclei frequency 7- to 8-fold above the air-only control values. Female rats examined from the 2% CF_3I group did not show an increase in the mean percentage of micronucleated cells compared to the control value (Table 14). Bone marrow toxicity (indicated by a statistically significant reduction in the ratio of number of polychromatic

Table 14. Micronuclei Induction by CF_3I in Rat Bone Marrow Erythrocytes

Group	Micronucleated Cells (%)[a]	Ratio
	Male Rats 30 Days	
Control (3)[b]	0.23 ± 0.05	1.00
4 % (5)	0.64 ± 0.10	2.74
8% (4)	0.90 ± 0.12	3.86
	Male Rats 90 Days	
Control (2)	0.25 ± 0.05	1.00
2 % (5)	0.60 ± 0.09	2.40
4 % (5)	1.06 ± 0.17	4.24
8 % (5)	1.38 ± 0.27	5.52
	Female Rats 30 Days	
Control (3)	0.20 ± 0.08	1.00
2 % (5)	0.20 ± 0.06	1.00
4 % (5)	0.70 ± 0.13	3.50
8 % (4)	0.98 ± 0.18	4.88
	Female Rats 90 Days	
Control (2)	0.30 ± 0.10	1.00
2 % (5)	0.58 ± 0.16	1.93
4 % (5)	0.78 ± 0.16	2.60
8 % (5)	1.30 ± 0.24	4.33

[a]Mean ± SD.
[b](N)

erythrocytes to number of normochromatic erythrocytes; PCE/NCE) was observed in male and female rats exposed to 4 or 8% CF_3I and in female rats exposed to 2% CF_3I (Table 15).

Table 15. PCE/NCE Ratio Evaluation

Group	PCE/NCE[a]	Ratio
Male Rats 30 Days		
Control (3)[b]	0.66 ± 0.19	1.00
4 % (5)	0.47 ± 0.05	0.72
8% (4)	0.50 ± 0.03	0.75
Male Rats 90 Days		
Control (2)	0.57 ± 0.00	1.00
2 % (5)	0.35 ± 0.07	0.61
4 % (5)	0.28 ± 0.03	0.49
8 % (5)	0.24 ± 0.04	0.43
Female Rats 30 Days		
Control (3)	0.75 ± 0.07	1.00
2 % (5)	0.67 ± 0.07	0.90
4 % (5)	0.63 ± 0.05	0.85
8 % (4)	0.38 ± 0.04	0.50
Female Rats 90 Days		
Control (2)	0.62 ± 0.03	1.00
2 % (5)	0.31 ± 0.05	0.50
4 % (5)	0.27 ± 0.02	0.44
8 % (5)	0.25 ± 0.05	0.40

[a]Mean ± S.D.
[b](N)

90 Days. CF_3I exposure increased the micronuclei frequency in polychromatic erythrocytes of male rats by 2.4-, 4.2- and 5.5-fold and of female rats by 1.9-, 2.6- and 4.3-fold at concentrations of 2, 4 and 8%, respectively (Table 14). The PCE/NCE ratios, compared to control values, were reduced by 39, 51 and 57% in male rats and by 50, 56 and 60% in female rats of the 2, 4 and 8% CF_3I groups, respectively (Table 15).

Pathology

30 Days. At necropsy, there were no exposure-related or clinically significant gross lesions. Microscopically, the prevalence of rhinitis was 100% in the 8% CF_3I-exposed male and female rats (Table 16). This lesion was described as mild mucopurulent rhinitis, characterized by abundant intraluminal accumulation of mucus admixed with degenerate neutrophils. Two of five male rats of the 4% group had similar, but milder lesions in the nasal turbinates (Table 17), while two of five female rats (4% group) had minimal olfactory epithelial necrosis. CF_3I-exposed male rats of the 8% group showed a marked degeneration and loss of spermatogonia, with dramatic loss of spermatids (Table 16). Aspermia was observed and shrunken seminiferous tubules were lined by a single layer of Sertoli cells, which appeared normal. Epididymal lumina were filled with sloughed spermatogonia admixed with a few degenerative spermatids. Testicular lesions were similar, but milder in the 4% CF_3I group of male rats. No additional exposure-related microscopic lesions were observed.

Table 16. Incidence Summary of Selected Microscopic Lesions of Male F-344 Rats Following 30 Days of Treatment with CF_3I

Organ/Lesion	Control	Low	Medium	High
Nasal Turbinates (N)	5	0	5	5
Rhinitis (%)	0	---	40	100[a]
(severity)[b]	0.0	---	0.8	3.0[a]
Testis (N)	5	0	5	5
Atrophy and degeneration (%)	0	---	100[a]	100[a]
(severity)	0.0	---	2.0[a]	4.0[a]

[a]Significantly different from control, $p<0.01$.
[b]Mean grades of severity based on: 0 = Normal; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Marked; 5 = Severe.

Table 17. Incidence Summary of Selected Microscopic Lesions of Female F-344 Rats Following 30 Days of Treatment with CF_3I

Organ/Lesion	Control	Low	Medium	High
Nasal Turbinates (N)	5	5	5	5
Rhinitis (%)	0	0	0	100[a]
(severity)[b]	0.0	0.0	0.0	2.6[a]
Necrosis (%)	0	0	40	0
(severity)	0.0	0.0	0.4	0.0

[a]Significantly different from control, $p<0.01$.
[b]Mean grades of severity based on: 0 = Normal; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Marked; 5 = Severe.

90 Days. At necropsy, there were no exposure-related or clinically significant gross lesions. The rhinitis noted at 30 days was no longer present. However, 56% of the high-exposure male rats exhibited minimal multifocal olfactory epithelial necrosis (Table 18). Similar changes were present in the 8% CF_3I-exposed female rats, though at a lower incidence (Table 19). This lesion was characterized by sloughing of scattered, small groups of epithelial cells, with shrunken cytoplasm and pyknotic nuclei; however, there was no intraluminal mucopurulent material.

Table 18. Incidence Summary of Selected Microscopic Lesions of Male F-344 Rats Following 90 Days of Treatment with CF_3I

Organ/Lesion	Control	Low	Medium	High
Nasal Turbinates (N)	10	8	10	9
Rhinitis (%)	0	13	0	0
(severity)[a]	0.0	0.1	0.0	0.0
Necrosis (%)	0	13	10	56[b]
(severity)	0.0	0.1	0.1	0.6
Thyroid (N)	10	8	10	9
Dilated follicles (%)	0	13	10	100[c]
(severity)	0.0	0.1	0.1	1.1[c]
Testis (N)	10	8	10	9
Atrophy and degeneration (%)	0	38	30	78[c]
(severity)	0.0	1.1	0.9	2.2[c]
Epididymis (N)	10	7	10	9
Epididymitis (%)	0	14	40	0
(severity)	0.0	0.4	0.7	0.0

[a]Mean grades of severity based on: 0 = Normal; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Marked; 5 = Severe.
[b] Significantly different from control, $p<0.05$.
[c] Significantly different from control, $p<0.01$.

Mild testicular degeneration and atrophy were noted in 78% of the high-exposure male rats (Table 18). The severity of this lesion was less when compared to the observations noted at Study Day 30. Minimal degeneration of the testes was noted also in the 4 and 2% CF_3I exposure groups. Epididymal sperm granulomas were present in 40% of the mid-level and 14% of the low-level CF_3I-exposed rats; however, this lesion was not present in the 8% CF_3I or control male rats.

Table 19. Incidence Summary of Selected Microscopic Lesions of Female F-344 Rats following 90 Days of Treatment with CF_3I

Organ/Lesion	Control	Low	Medium	High
Nasal Turbinates (N)	9	9	10	10
Necrosis (%)	11	22	0	40
(severity)[b]	0.1	0.2	0.0	0.4
Thyroid (N)	9	10	10	9
Dilated follicles (%)	0	10	20	100[a]
(severity)	0.0	0.1	0.2	1.0
Spleen (N)	8	0	0	10
Hemosiderin (%)	63	---	---	40
(severity)	0.6	---	---	0.5

[a]Significantly different from control, $p<0.01$.
[b]Mean grades of severity based on: 0 = Normal; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Marked; 5 = Severe.

All male and female rats from the 8% CF_3I exposure group exhibited a mild, diffuse increase in thyroid follicular colloid content (Tables 18 and 19). No follicular lining cell hypertrophy or hyperplasia was observed. Similar changes were noted, but with much lower incidence, in mid- and low-exposure animals. Computerized morphometric image analysis of the observed follicular colloid confirmed that there was a treatment-related increase in follicular lumen area of CF_3I-exposed rats (Table 20). However, the increase was not concentration-related, and statistical significance was observed in the high-exposure female rats only.

For the remaining tissues examined, histologic lesions noted were considered to be commonly observed incidental findings unrelated to CF_3I exposure. In some animals, there was mild to minimal degenerative cardiomyopathy consisting of scattered bundles of degenerative myocytes, occasionally infiltrated by low numbers of macrophages and lymphocytes. Male rats exhibited some histologic evidence of renal tubular hyaline droplet formation and occasional mild tubular mineralization.

Table 20 Follicular Area[a] of Thyroids of Male and Female F-344 Rats following 90-Days Inhalation of CF_3I

	Control	Low	Medium	High
Male	1395 ± 63	1515 ± 53	1607 ± 52	1587 ± 59
Female	1388 ± 47	1427 ± 45	1405 ± 49	1922 ± 67[b]

[a]$(Microns)^2$, Mean ± SEM, N = 993 to 1248.
[b]Significantly different from control, $p<0.05$.

SECTION IV

DISCUSSION

In this study, male and female F-344 rats were exposed to 8, 4, 2, or 0% CF_3I vapor, 2 h/day, 5 days/week for 13 weeks. Because of the high cost of the CF_3I test material and to keep study expenses reasonable, exposures were conducted in nose-only chambers where animals were placed in restraining tubes during the period of CF_3I inhalation. Exposure systems requiring animal restraint may cause animal stress (reviewed by Phalen *et al.*, 1984), such as excessive heat, decreases in body weight (Klimisch *et al.*, 1987), alterations in pulmonary function (Landry *et al.,* 1983) or suppression of pulmonary defenses (Jakab and Hemenway, 1989). The deaths observed in the present study were attributed to accidents for the restraint system employed. Rationale for this explanation include the observation of deaths in male rats only (the heavier gender), lack of concentration-related effect (deaths occurred in the low and high CF_3I concentration groups only), and absence of mortality upon the use of larger (and presumably less stressful) holding tubes for rats weighing more than 225 g. Further, all deaths occurred between Exposure Days 9 and 13. In the two-week nose-only exposure range-finding study with CF_3I (Kinkead *et al.,* 1995), no animal deaths were observed at vapor concentrations as high as 12%.

The testicular effects observed in the present study are suspect, in part, to be due to the heat stress associated with the use of nose-only exposure chambers. It is well recognized that in rats, the testis is exquisitely sensitive to hyperthermia-induced degeneration and atrophy (Haschek and Rousseaux, 1991). Recent studies at Haskell Laboratories with hydrofluorocarbon-143a (Frame *et al.,* 1992) compared the results of toxicity observed by either nose-only or whole-body exposure systems and concluded exposure design was a factor in the testicular lesions that were observed only in the nose-only chamber system. Further, the finding in the current study, that the severity of testicular degeneration and atrophy was considerably less in male rats sacrificed at 90 days compared to male rats killed at 30 days was associated closely with the size of the restraining tubes used and the timing of their use. However, the absence of both testicular atrophy and degeneration of spermatogonia in male rats of the low CF_3I concentration group (at 90 days) or air-only control group (at 30 and 90 days) suggest a CF_3I-induced effect at higher exposure concentrations.

Observations of lower body weights and mild to minimal inflammation in the nasal turbinates of male and female rats exposed to 8 or 4% CF_3I are common signs of toxicity indicative of inhalation studies conducted with mildly adverse chemicals at very high exposure concentrations. The measured endpoints of greatest concern, but not unexpected, are the lesions observed in the bone marrow and thyroid. CF_3I was positive in the Ames (Mitchell,

1995a) and mouse bone marrow erythrocyte micronucleus tests (Mitchell, 1995b), but was negative in the mouse lymphoma test (Mitchell, 1995c). The finding of induction of micronuclei in bone marrow PCEs in the present study extends the observation of an *in vivo* chromosomal effect to two mamalian species. However, the lack of histopathology, including any cell proliferative-type lesions in the numerous tissues observed in this study, places the concern of this genotoxic effect produced by CF_3I as equivocal.

The thyroid gland is a target organ in this study. Serum chemistry analysis provided support for the mechanistic hypothesis that CF_3I inhibits the enzyme iodothyronine 5'-deiodinase that is responsible for the conversion of T_4 to T_3, resulting in a decrease in T_3, a corresponding marked increase in rT_3, and a compensatory increase in TSH. The response of the thyroid gland to increased TSH levels is to increase T_4 production by the follicular cells (Capen, 1995). This physiologic event is manifested histologically by a marked decrease in follicular colloid content and increased height of follicular lining cells . Histologic alterations observed in the thyroid follicles in this study did not follow this histologic scenario, and in fact exhibited the opposite condition, with follicles being slightly increased in area (statistically significant in female rats of the 8% CF_3I group), and lined by flattened rather than columnar follicular cells. Similar observations were observed in studies with excess iodide in drinking water (Kanno *et al.*, 1994) and with FD&C Red No. 3 dye (Capen and Martin, 1989), and recent evidence (Capen, 1996) suggests that the presence of iodinated lipid molecules in the plasma membrane of thyroid follicular cells may modify receptor sensitivity to TSH, thereby decreasing the proliferative response of the cells to elevated TSH levels. In contrast, non-iodinated goitrogens (e.g., propylthiouracil) appear to decrease the formation of iodolipids, resulting in the classic proliferative response by follicular cells. In this study, the clinical and histopathologic results provide support for the expected response to a highly iodinated compound which inhibits 5'-deiodinase and results in the formation of iodolipids; however, further studies are required to confirm either hypothesis. Though toxicity concerns, including thyroid goiter and tumor development, exist for chemicals inducing a sustained increase in the secretion of pituitary TSH, rats and mice are highly sensitive species compared to humans to these pathological phenomena in the thyroid gland (Capen, 1996; McClain *et al.*, 1988).

Subchronic inhalation toxicity of CF_3Br, a chemical used widely for its fire extinguishant properties, was investigated in rats and dogs more than 40 years ago (Comstock *et al.*, 1953). Daily exposures for 18 weeks at an average concentration of 2.3% CF_3Br showed no signs of adverse effects and no pathological changes at necropsy. The present ACGIH TLV-TWA value of 1000 ppm (0.1% v/v) for CF_3Br was recommended to minimize the potential central nervous system and cardiovascular involvement observed in controlled studies performed in laboratory animals and humans (ACGIH, 1986). The epinephrine-induced cardiac sensitization NOAEL in

dogs is approximately 5% for CF_3Br (reviewed by Trochimowicz, 1975) compared to a NOAEL of 0.2% for CF_3I (Kenny *et al.*, 1995).

The results from this investigation showed definite signs of multiple organ toxicity in rats of the 8% group. Mild to minimal toxicity extended into rats of the 4 and 2% CF_3I exposure groups. Though NOAELs were observed for select target organs (e.g., testes and nasal turbinates), NOAELs were not apparent in all target organs examined (e.g., thyroid and bone marrow).

SECTION V

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Appendix A.

Listing of Tissues Taken for Histopathologic Examination

Gross lesions	Heart
Brain	Liver
Lungs (perfused)	Spleen
Trachea	Duodenum
Prostate	Spinal cord
Epididymides	Urinary bladder
Jejunum	Cecum
Ileum	Salivary glands
Esophagus	Stomach
Mandibular lymph nodes	Colon
Mesenteric lymph nodes	Rectum
Thymus	Sternum w/bone marrow
Kidneys	Sciatic nerve
Adrenals	Skeletal muscle (thigh)
Ovaries/Testes	Bone (femur including stifle
Pituitary	Thyroid w/parathyroid
Nasal turbinates	Zymbal gland
Pancreas	Lachrymal gland
Uterus	

Appendices B through M contain details on individual animal data and are not provided to minimize reproduction costs. The original set of these appendices will be maintained in the archives of the Toxic Hazards Research Unit, AL/OET, Wright-Patterson AFB, OH.